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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING MIDAZOLAM IN A HIGH CONCENTRATION

(57) Abstract: The present invention relates to the administration of midazolam. In particular, the invention provides new midazolam compositions for intranasal administration. These compositions contain midazolam in a high concentration of at least 35mg/ml.



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## Pharmaceutical Compositions Comprising Midazolam in a High Concentration

### Description

5

The present invention relates to the administration of benzodiazepines such as midazolam. In particular, the invention provides improved midazolam compositions for intranasal administration in a high concentration.

10 Midazolam is a potent benzodiazepine derivative with sedative, anxiolytic, hypnotic, amnesic, anticonvulsant and muscle relaxant pharmacological properties. Because of the basicity of this molecule, it is possible to prepare salts (e.g., with hydrochloric, maleic and lactic acid) which are soluble in water. From these salts, stable aqueous solutions with a pH of 3.5 can be made for intravenous and intramuscular injections  
15 of midazolam (Smith et al., 1981; Gerecke, 1983; Persson et al., 1988). Following administration by injection, midazolam is characterized by a fast onset of action as well as short duration of action, due to its rapid metabolic inactivation by liver enzymes. Midazolam is about twice as potent as the classical benzodiazepine diazepam (Randell and Kytä, 1998).

20

For drug administration in general, the oral route is probably the most popular route. However, this mode of administration is not suitable for midazolam, as orally delivered midazolam is extensively degraded by first-pass elimination and has also been found to be a substrate for the intestinal drug efflux transporter (Allonen et  
25 al., 1981; Crevoisier et al., 1983; Tolle-Sander et al., 2003). The oral absorption of midazolam is therefore relatively low and variable, with absolute bioavailabilities ranging from just 15 to 27% in children (Payne et al., 1989) and from 31 to 72% in healthy adults (Allonen et al., 1981; Heizmann et al., 1983).

30 Other disadvantages associated with the oral administration of midazolam are the slow onset of action and the observed low peak plasma concentrations. These disadvantages are also observed when midazolam is administered rectally (Saint-Maurice et al., 1986; Malinovsky et al., 1993, 1995).

Rapid onset of the therapeutic action of midazolam can be achieved by intravenous and intramuscular injection (Taylor et al., 1986; Burstein et al., 1997; Uygur-Bayramicli et al., 2002). However, this mode of administration has a number of  
5 obvious disadvantages which make it unattractive. For example, injections are painful and not well accepted by the patients, particularly not by young children.

In light of the foregoing, intranasal delivery of midazolam is a very attractive alternative mode of administration.

10

Intranasal drug administration is painless, results in rapid drug absorption and avoids hepatic first-pass elimination. An additional advantage is the ease of administration, leading to better patient compliance. The mucosa of the nasal cavity is constructed from a highly vascularized tissue covered by a pseudostratified  
15 columnar epithelium with numerous microvilli. It has a much higher permeability than other mucosal surfaces, including the sublingual area, various regions of the gastrointestinal tract, and the buccal mucosa. In addition, nasal midazolam administration results in pharmacokinetic and pharmacodynamic profiles, which are very similar to those observed after intravenous injections (Walbergh et al., 1991;  
20 Björkman et al., 1997; Burstein et al., 1997).

A number of studies have been reported which demonstrate the beneficial effects of intranasally administered midazolam in patients, both in children and adults. When administered in this way, midazolam appears to have a rapid onset of action (about  
25 10 minutes) and a relatively short duration of action (30 to 60 minutes).

Nasal midazolam at dosages of 0.2 mg/kg has been shown to have sedative and anxiolytic effects in children undergoing various diagnostic and minor surgical procedures, and none of the children had clinical signs of respiratory depression, bradycardia or other side effects (Wilton et al., 1988; Karl et al., 1992; Davis et al.,  
30 1995). Comparable clinical results have also been published for nasal midazolam in dosages of 0.3 and 0.4mg/kg (Theroux et al., 1993; Malinovsky et al., 1995; Kogan

et al., 2002). No additional benefit is found for the midazolam dose of 0.3 mg/kg compared to the lower dose of 0.2 mg/kg (Wilton et al., 1988; Davis et al., 1995).

Nasal midazolam (0.2mg/kg) also suppresses acute seizures and improves the EEG  
5 background in epileptic children (O'Regan et al., 1996; Lahat et al., 1998, 2000). As  
stated by O'Regan et al., (1996): "The EEG technicians welcomed the intranasal  
administration of benzodiazepines. Their time was no longer wasted in waiting for  
medical staff to achieve satisfactory intravenous access for the drugs. Often there is  
a difficulty in siting a butterfly needle or cannula, causing the child to cry, become  
10 very restless, or to pull the leads off". Moreover, Lahat et al. (2002) concluded that  
intranasal midazolam could be provided not only in medical centres but, with  
appropriate instruction, by the parents of children with febrile seizures at home.

In adult patients undergoing gastrointestinal endoscopy, intranasal administration of  
15 midazolam (0.1mg/kg) is used for the induction of sedation and the nasal route has  
been shown to cause fewer side effects than intravenous injection (Uygur-Bayramicli  
et al., 2002). Nasal midazolam is also effective in the short-time management of  
seizures in adolescent and adult patients with severe epilepsy (Scheepers et al.,  
2000). In this clinical study the midazolam dosage used was 5 and 10mg in patients  
20 weighing less than 50kg and more than 50kg, respectively. Case reports have also  
shown the sedative effect of midazolam (0.25mg/kg) in an adult patient with a  
seizure disorder (Cheng, 1993) and the seizure-terminating activity of nasal  
midazolam (dose of 4mg) in an adult epileptic woman (Kendall et al., 1997).

25 Whilst the above discussed studies have demonstrated the efficacy of nasally  
administered midazolam, it should be noted that in all clinical studies mentioned  
above the commercially available injection solutions, containing midazolam at  
concentrations of 5mg/ml (Dormicum®, Hoffmann-La Roche, Switzerland), were  
used. The use of solutions with this concentration of midazolam requires very large  
30 volumes of liquid to be applied intranasally, ranging from 1ml in children to even 4-  
5ml in adults.

When such large volumes of liquid are administered intranasally, a large portion of the volume actually drops out of the nose and/or will be swallowed, resulting, at best, in part of the dose being administered orally rather than nasally. This oral midazolam absorption is clearly shown by Burstein et al. (1997). As discussed  
5 above, the orally administered midazolam will have a significantly reduced therapeutic effect compared to the intranasally administered midazolam.

The nasal administration of such large volumes of solution also accounts for a number of unpleasant side-effects sometimes experienced by patients, including  
10 lacrimation, burning sensations, irritation in the nose and throat, and general discomfort (Lugo et al., 1993; Burstein et al., 1997; Kogan 2002). In addition, treatment failure can occur due to the inadequate technique of delivering unphysiologically large volumes of the midazolam solution (Scheepers et al., 2000).

15 A further problem is clearly the loss of a large proportion of the composition and of the midazolam, which leads to inconsistent and unpredictable amounts of midazolam being absorbed.

It is therefore clear that the use of commercially available midazolam injection  
20 solutions for intranasal midazolam administration is inefficient and unpleasant for the patients, due to the necessary large volumes applied. This can lead to reduced nasal bioavailability and ineffective plasma peak concentrations of midazolam and therefore to an insufficient therapeutic efficacy.

25 For efficient and comfortable nasal drug delivery, volumes of about 200 $\mu$ l (100 $\mu$ l into each nostril) are normally the maximum that should be administered to a patient. This implies that there is an urgent need for the availability of nasal formulations with highly increased midazolam concentrations in comparison with the midazolam injection solutions.

30

A few nasal midazolam formulations have been developed which seek to reduce the total volume of liquid to be delivered intranasally to the patients. These formulations are described in detail in Table 1 below.

Table 1 Nasal Midazolam Formulations

Reference	Composition	pH
Lui et al. (1991)	Midazolam HCl 11.1mg/ml Methocel 1.5% (w/v) Water	about 4
Loftsson et al. (2001)	Midazolam base 17mg/ml SBE $\beta$ CD 14% (w/v) HPMC 0.10% (w/v) Benzalkonium chloride 0.02% (w/v) EDTA 0.1% (w/v) Phosphoric acid 0.43% (v/v) Water	4.3
Knoester et al. (2002a)	Midazolam HCl 30.9mg/ml Benzyl alcohol 1% (v/v) = 10.46mg/ml Propylene glycol 25% (v/v) = 259mg/ml Water	4

HPMC, hydroxypropyl methylcellulose 4000

SBE $\beta$ CD, sulfobutylether- $\beta$ -cyclodextrin sodium salt (Captisol®)

5

The midazolam formulation used in Lui et al. (1991) is an acidic solution of midazolam hydrochloride (11.1mg/ml) and 1.5% methocel as a viscosity-enhancing agent. It is prepared by freeze-drying the commercially available midazolam injection solution. The dried product is dissolved in water and mixed with the appropriate volume of a 7.5% methocel aqueous solution.

10

The formulation has been tested for nasal midazolam absorption in dogs, and not in human subjects. However, nasal administration of a total volume of 200 $\mu$ l of this formulation will not achieve therapeutically effective midazolam plasma levels in humans, because the midazolam concentration in this formulation is far too low.

15

The nasal formulation used by Loftsson et al. (2001) comprises midazolam hydrochloride (17mg/ml) with 14% sulfobutylether- $\beta$ -cyclodextrin sodium salt (SBE $\beta$ CD; Captisol®) as solubilizer in an acidic solution at pH 4.3. The presence of 0.1% hydroxypropyl methylcellulose (HPMC) has an additional solubilizing effect.

5 This formulation also contains 0.02% benzalkonium chloride and 0.1% EDTA as preservatives.

Acute intranasal administration of this midazolam formulation in healthy volunteers (100-160 $\mu$ l into each nostril) is associated with mild to moderate transient irritation

10 of the nasal mucosa (Gudmundsdottir et al., 2001).

A further disadvantage associated with this formulation is that the preservative mixture of 0.02% benzalkonium chloride/0.1% EDTA inhibits the ciliary movement *in vitro* and is classified as ciliostatic (Merkus et al., 2001). Also the use of the high

15 Captisol® concentration (14%) required to solublize midazolam will also lead to a strong ciliostatic effect.

It is known that ciliary beating is the major factor in normal functioning of the nasal mucociliary clearance, which is a very important defence mechanism of the

20 respiratory tract (Martin et al., 1998). Nasal administration of the midazolam formulation of Loftsson et al. (2001) can therefore be expected to disturb the mucociliary clearance of the patients. More importantly, the midazolam concentration of this nasal formulation is too low to provide adequate therapeutic efficacy of the drug.

25 The intranasal midazolam formulation used by Knoester et al. (2002a, 2002) and Tenk et al. (2003) consists of midazolam hydrochloride (30.9mg/ml) in a mixture of 25% (v/v) propylene glycol and water (pH 4). It also contains 1% (v/v) benzyl alcohol as a preservative. A dose of 5mg midazolam base is delivered by two sprays

30 of 90 $\mu$ l and, for a dose of 10mg midazolam base, 4 sprays of 90 $\mu$ l are needed (providing a total dose of 360 $\mu$ l).

The use of this formulation for intranasal midazolam administration in healthy volunteers and in epilepsy patients, providing a dose of 5mg or 10mg (90-180µl in each nostril), causes nasal irritation, lacrimation and irritation of the throat in almost all subjects, as well as a bitter taste (Knoester et al., 2002; Tenk et al., 2003).

5 In *in vitro* experiments with ciliated tissue, this midazolam formulation has been shown to be ciliostatic, probably due, in particular, to the presence of 25% propylene glycol and 1% benzyl alcohol (Merkus et al., 2001). It is evident from these studies that the volume of the formulation used to administer a dose of 5 and 10mg via the nose is very large (two and four nasal sprays), and this is probably the

10 cause of many of these adverse side effects. These adverse effects could prohibit the use of this formulation in clinical practice.

In light of the foregoing, it is clear that there is the need for a midazolam formulation which is specifically formulated for intranasal administration, in order

15 to overcome all of the various disadvantages associated with the known formulations which are administered intranasally. It is therefore an aim of the present invention to provide a formulation with a high enough midazolam concentration to allow adequate doses of midazolam to be efficiently and comfortably administered via the intranasal route in a small volume. The

20 formulation should also cause as little irritation as possible and have as high a bioavailability as possible. Finally, the formulation should have a similar or reduced ciliostatic effect in *in vitro* experiments, compared to the known nasal formulations.

According to a first aspect of the present invention, a pharmaceutical composition

25 is provided, wherein the composition is a solution comprising midazolam in a concentration of at least 35mg/ml (based on the free base form of midazolam), and a solubilizer. The composition may contain midazolam either in the form of its free base or a pharmaceutically acceptable salt thereof.

30 The compositions according to the present invention are preferably suitable for intranasal administration.



In one embodiment of the invention, the concentration of midazolam is at least 40mg/ml, or at least 50mg/ml. The midazolam concentration may also be less than 100mg/ml, less than 75mg/ml or less than 60mg/ml. In a preferred embodiment, the midazolam concentration is 35-75mg/ml.

5

In a particularly preferred embodiment of the present invention, the composition is an aqueous solution. It is surprising that the solutions with such high midazolam concentrations may be formed including water, as it is well documented that midazolam is only poorly soluble in water.

10

However, once the problems associated with forming an aqueous solution of a high concentration of midazolam have been overcome, the solution has a number of surprising benefits.

15 In the present invention, the problem of the poor solubility of midazolam in water is overcome by the inclusion in the solution of a solubilizer. Particularly effective solubilizers include propylene glycol, glycerol, polyethylene glycol, povidone and ethanol, or combinations thereof. The inclusion of solubilizers not only enables the formation of an aqueous midazolam solution, but also allows that solution to have a  
20 high midazolam concentration. The preferred solubilizers for inclusion in the compositions of the present invention are discussed in greater detail below.

Thus, it is clear that significant formulatory hurdles had to be overcome in order to arrive at the high concentration midazolam solutions of the present invention. In  
25 particular, there was the prejudice against including water in a high concentration midazolam solution.

The prior art does not disclose nasal midazolam formulations having such high midazolam concentrations. The reason for this is that it was previously considered  
30 that the limited solubility of midazolam meant that concentrations of up to around 30mg/ml was the maximum possible (see Table 1). However, this is not true, especially when using propylene glycol alone as the solubilizer or propylene glycol in combination with glycerol and optionally one or more of polyethylene glycol,

- 9 -

povidone, and ethanol. It was also considered in the prior art that the formulations for nasal administration should have a pH of no less than about 4, as the intranasal administration of a formulation with a lower pH was thought to be too uncomfortable, due to irritation. These prejudices have led the skilled person to  
5 administer large volumes intranasally, leading to the above discussed problems.

Contrary to the common opinion of the skilled person, the nasal administration of formulations having a pH lower than 4 is not unacceptable to patients. More importantly, the lower pH allows greater amounts of midazolam to be dissolved,  
10 allowing composition with higher concentrations of midazolam to be prepared which, in turn, enables smaller volumes of formulation to be administered.

The high midazolam concentration has a number of surprising advantages. Firstly, as discussed above, it means that smaller volumes of the solution can be  
15 administered in order to achieve a desired therapeutic effect. This reduces the wastage due to varying amounts of the composition being swallowed or dropping out of the nose, so that more of the administered midazolam is properly absorbed and has the desired therapeutic effect. This also reduces the unpleasant taste and irritation which accompanies swallowing of the nasal composition. It also increases  
20 the dose consistency and predictability. This, in turn, enables one to achieve a specific therapeutic effect, as the plasma levels achieved following intranasal administration will be predictable and controllable. As discussed below, different midazolam plasma levels result in different therapeutic effects on the patient. The midazolam compositions for intranasal administration disclosed in the prior art do  
25 not result in consistent or predictable plasma levels and so do not permit accurate dosing to achieve a specific therapeutic effect.

The high midazolam concentration also means that some therapeutic effects which were previously difficult or impossible to achieve using known midazolam  
30 compositions can now be reliably achieved. If one can administer just 50-100 $\mu$ l per nostril instead of 2, 4 or even 10 times that volume per nostril, this will clearly be beneficial, especially if the patient is nervous or is a crying child or the like. Therefore, in one embodiment of the invention, the composition provides a

therapeutically effective dose of midazolam in a total volume of up to about 200 $\mu$ l. Preferably, the composition provides a therapeutically effective dose of midazolam in a volume of up to about 100 $\mu$ l, it being possible to administer this dose to each nostril.

5

Another benefit associated with administering a smaller volume of the composition intranasally is that it results in a smaller area of deposition within the nose. This localised administration within the nose means that any transient irritation will also be localised and limited to a small area within the nose and throat. This, once again, reduces the discomfort experienced by the patient.

10

Additionally, the high midazolam concentration has also been demonstrated to enhance diffusion of the active agent through the nasal epithelium, resulting in faster absorption compared to that observed with solutions having lower midazolam concentrations. This not only means a faster onset of the therapeutic effect, but also a reduction in the time for which the active agent is in contact with the nasal epithelium. Again, this will reduce the patient's discomfort, as the midazolam itself is an irritant. Also, less of the midazolam formulation will reach the throat and so there is less chance for irritation by the formulation ingredients and for experiencing the bitter taste of midazolam.

15

In one embodiment of the invention, the midazolam included in the composition is a salt of midazolam, such as midazolam hydrochloride, midazolam maleate or midazolam lactate. Preferably, the composition comprises midazolam hydrochloride.

20

In a preferred embodiment of the invention, the solubilizer comprises propylene glycol. Propylene glycol is a good solubilizer for midazolam, especially when the midazolam is to be formulated as an aqueous solution. In addition to the propylene glycol, the solubilizer may further comprise one or more of the following: glycerol, polyethylene glycol, povidone, and ethanol.

25

30

In an alternative embodiment of the invention, the solubilizer comprises glycerol, another good solubilizer for midazolam when an aqueous solution is to be formed. In addition to the glycerol, the solubilizer may further comprise one or more of the following: propylene glycol, polyethylene glycol, povidone, and ethanol.

5

In a particularly preferred embodiment of the invention, the composition is a solution of midazolam comprising 90-10%, 80-20%, 70-30%, 60-40% or 40-50% (v/v) solubiliser, preferably propylene glycol. The composition preferably also comprises 10-90%, 20-80%, 30-70%, 40-60% or 50-60% (v/v) water. Furthermore,  
10 the composition preferably comprises 40-75 mg/ml midazolam. A composition comprising 40-50% (v/v) propylene glycol and 50-60% (v/v) water is considered as being particularly advantageous.

In one embodiment of the invention, the composition comprises a combination of  
15 propylene glycol and glycerol. Glycerol has a sweet taste and, in addition to acting as an excellent solubilizer, it also serves to mask the taste of the midazolam, should some of the solution go down the back of the throat of the patient.

Propylene glycol and glycerol have further advantages.. Compositions comprising  
20 solubilizers containing propylene glycol (>15% v/v) and/or glycerol (>20% v/v) do not need to include a preservative, because it is known from the literature that these concentrations of glycerol and of propylene glycol act as antimicrobial preservatives (Handbook of Pharmaceutical Excipients, Third Edition, The Pharmaceutical Press, London 2000).

25

Propylene glycol, glycerol, polyethylene glycol and povidone are also attractive solubilizers for use in a nasal solution because they do not have a strong adverse effect on ciliary movement. In *in vitro* experiments, according to a previously published method (Merkus et al, 2001), the effect of four different solubilizers [25%  
30 propylene glycol, 15% glycerol, 25% polyethylene glycol 400 and 5% povidone], dissolved in a Locke-Ringer solution, on the ciliary beat frequency (CBF) of ciliated tissue taken from chicken embryo tracheal tissue was measured. All four compounds showed a decrease in CBF after 15 minutes. However, after rinsing with Locke-

Ringer solution, the effects on CBF appeared to be completely reversed within 20 minutes.

5 The solubilizers used in the compositions of the present invention should cause as little irritation as possible when administered *in vivo*, and preferably no irritation at all. Whilst transient and mild irritation can be tolerated by patients, this should be kept to a minimum in order to avoid unnecessary discomfort.

10 The preferred solubilizers used in the present invention and discussed above will not cause unnecessary irritation upon intranasal administration.

Despite the reduction in the amount of swallowed composition achieved by using the compositions of the present invention, it is nevertheless possible that a very small part of the midazolam dose will reach the throat, which may lead to a bitter  
15 taste. Therefore, in another embodiment of the invention, one or more sweeteners are included in the composition, to mask the bitter taste of midazolam. According to this embodiment, the formulation may comprise midazolam in a concentration of at least 35mg/ml, a solubilizer and a sweetener.

20 Suitable sweeteners for inclusion in the compositions of the present invention include saccharin and saccharin alkali salts (which may be included in an amount of about 0.1-5% w/v), aspartame (which may be included in an amount of about 0.1-5% w/v), acesulfame K and cyclamate.

25 Further additional components which may be included in the compositions of the present invention include flavouring agents, preservatives, buffers, stabilising agents and pH adjusting agents, known from the pharmaceutical literature (Martindale 33rd edition, The Pharmaceutical Press, London 2002). In a preferred embodiment, the composition is free from any buffers.

30

Suitable flavouring agents include vanilla (vanillin), mint, raspberry, orange, lemon, grapefruit, caramel, cherry flavours and combinations of these.

Suitable stabilising agents include cyclodextrins such as beta-cyclodextrin (which may be included in an amount of about 1%) and derivatives of beta-cyclodextrin (which may be included in an amount of about 1-4%).

- 5 In an alternative embodiment, the compositions according to the present invention are free from any preservatives and/or stabilising agents. In another embodiment, the composition is free from benzyl alcohol

In a yet further embodiment of the invention, the compositions further comprise a  
10 viscosity enhancing agent. Viscosity enhancing agents are well known to the person skilled in the art from the pharmaceutical literature and will include agents such as cellulose derivatives. Enhancing the viscosity of the solution can enhance the delivery of the midazolam. Viscosity enhancing agents such as cellulose derivatives may also serve to increase the stability of the solutions.

15

The enhanced absorption of midazolam using the compositions according to the present invention means that the compositions of the invention may be free from any absorption enhancers.

- 20 The pH of the composition is preferably within the range of 2.5 to 7. In one embodiment, the pH of the composition is less than 4, and is preferably greater than 2.5. More preferably, the pH of the composition is between 3 and 4. Particularly preferably, the pH is around 3. Despite there being a general prejudice against compositions for nasal administration having such a low pH value, it has  
25 been found that there are no adverse effects or disadvantages associated with a composition having a pH in this range. Indeed, the midazolam is more soluble at lower pHs, making it easier to formulate solutions with high midazolam concentrations.

- 30 A pharmaceutically acceptable acid may be added to the solution in order to adjust the pH.

The free midazolam base is rather lipophilic with a partition coefficient between octanol and phosphate buffer (pH 7.5) of about 475. Therefore, the aqueous solubility of the midazolam base at neutral pH is too low to prepare suitable midazolam formulations and for this purpose midazolam salts (e.g., with  
5 hydrochloride) have to be used. Ionization of a drug will increase its aqueous solubility. In acidic solutions, midazolam as well as other 1,4-benzodiazepines are known to undergo reversible and pH-dependent ring-opening through the formation of aldehyde or ketone and a primary amine (Gerecke, 1983; Olivier et al, 2001; Loftsson et al., 2001). In the commercially available intravenous solutions of  
10 midazolam (5 mg/ml) with a pH of 3.3 to 3.5 the drug consists of 80-85% in the ring-closed form and 15-20% in the ring-open form (Gerecke, 1983). In this solution the ring-open form is considered as a prodrug of midazolam, because the ring is completely closed when the pH is increased to 7.4.

15 Intranasal administration of midazolam is characterized by rapid midazolam absorption, reaching maximum plasma concentrations in 5-15 minutes. The drug is subsequently eliminated from the blood circulation with half-lives ranging between 1 and 2.4 hours in children and healthy adults, which are not substantially different from that after intravenous injection of midazolam (Rey et al., 1991; Björkman et  
20 al., 1997; Burstein et al., 1997; Loftsson et al., 2001; Knoester et al., 2002; Tenk 2003).

Using the available midazolam injection solutions for intranasal midazolam delivery in children, healthy volunteers and adult surgical patients, mean absolute  
25 bioavailabilities of 50, 55 and 83% respectively, have been reported (Rey et al., 1991; Burstein et al., 1991; Björkman et al., 1997).

Examples of compositions according to the present invention are set out below.

### 30 Example 1

Midazolam HCl corresponding to 35-75mg/ml midazolam (free base)

Propylene glycol q.s. (in an amount sufficient to solubilize midazolam)

Water

Optionally, one or more of the following additional components may be added:  
polyethylene glycol, glycerol, povidone, ethanol, sweetener, flavouring substance,  
preservative, pH adjusting agent and stabilizing agents.

5

This composition is preferably formulated as a nasal spray or nasal drops or liquid  
for children and adults with a volume of 50-100 $\mu$ l, for intranasal administration.

The composition has a pH of between 2.5 and 7, preferably between 3 and 4.

#### 10 Example 2

Midazolam HCl corresponding to 35-75mg/ml midazolam

Propylene glycol 5-50% (v/v)

Glycerol 5-50% (v/v)

Polyethylene glycol 5-50% (v/v)

15 

Povidone 1-20% (w/v)

Water

The composition is formulated as a nasal spray or nasal drops or liquid with a  
volume for children and adults of 50-100 $\mu$ l.

20 

The pH of the solution should be between 2.5 and 7, preferably between 3 and 4.

#### Example 3

Midazolam HCl corresponding to 35, 40, 45 or 50 mg/ml midazolam

Propylene glycol 15-30% (v/v)

25 

Glycerol 15%-30% (v/v)

Saccharin sodium 10-50mg/ml

Water

The volume for intranasal administration is 50-100 $\mu$ l.



The pH of the solution should be between 2.5 and 7, preferably between 3 and 4.

#### Example 4

Midazolam HCl corresponding to 35, 40, 45 or 50 mg/ml midazolam

Propylene glycol 20-50% (v/v)

5 Povidone 1-10% (w/v)

Water

The volume for nasal administration is 50-100 $\mu$ l.

10 The pH of the solution should be between 2.5 and 7, preferably between 3 and 4.

#### Example 5

Midazolam HCl corresponding to 50 g/ml midazolam

45% (v/v) Propylene glycol

15 55% (v/v) Water

The pH of this solution has been adjusted to 3.

The intranasal midazolam solutions according to the present invention, providing to the subject a dose of 0.2mg/kg bodyweight is an interesting new route of drug  
20 administration.

According to a second aspect of the present invention, the compositions according to the first aspect may be used in the following situations:

- 1) as sedative and anxiolytic agents for children undergoing diagnostic and  
25 surgical procedures;
- 2) as sedative and anxiolytic agents for adults undergoing gastrointestinal endoscopy and other diagnostic procedures;
- 3) as treatment of acute epileptic and febrile seizures in children in medical centres and at home; and
- 30 4) as acute management to treat seizures in adults with severe epilepsy in medical centres and at home.

Conscious sedation using intranasal midazolam is a particularly attractive pre-operative technique which avoids the dangers and inconvenience of general anaesthesia in children and adults alike. Also, the use of midazolam in epilepsy sufferers is well documented in many clinical studies.

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A good correlation between plasma levels and pharmacodynamic responses has been established for midazolam in a clinical study in which patients, undergoing abdominal surgery, received an intravenous midazolam infusion (Persson et al., 1988). The results are summarized as follows: (1) midazolam plasma concentrations  
10 from 75ng/ml to a range of 150 to 200ng/ml are able to induce pronounced sedation and partial amnesia; (2) at plasma concentrations of 150 to 200ng/ml the sleeping patients are arousable; and (3) midazolam plasma levels of 250 to 300ng/ml are required to achieve satisfactory hypnotic effects during surgery. From many publications it is also evident that the plasma threshold concentration of midazolam  
15 for the induction of conscious sedation is in the order of 40 to 50ng/ml (Allonen et al., 1981; Crevoisier et al., 1983; Persson et al., 1988).

Intranasal delivery of midazolam at dosages of 0.2 to 0.25mg/kg body weight can reach mean peak plasma concentrations ranging from 100 to 185ng/ml in children  
20 and adults (Rey et al., 1991; Malinovsky et al., 1993; Burstein et al., 1997). In these clinical studies therapeutically effective plasma concentrations of midazolam are manifest as rapidly as 3 minutes after nasal administration and are maintained for about 1 hour. This relationship between plasma levels and clinical effect of midazolam is derived from nasal delivery studies using the commercial midazolam  
25 injection solution, and is also valid for nasal administration of midazolam in more concentrated solutions. For example, Tenk et al. (2003) administered midazolam intranasally in epilepsy patients at dosages of 5 and 10mg/patient (equivalent to about 0.06 and 0.12mg/kg, respectively), using the midazolam formulation of Knoester et al. (2002a, 2002). Maximum plasma concentrations of 73 and 140ng/ml  
30 are reached in 5 to 10 minutes, and for both nasal midazolam dosages the sedative effects in the patients last for 45 to 60 minutes after administration.

A clear relationship between plasma midazolam concentrations and its clinical effect is not always well established. Gudmundsdottir et al. (2001) did a pharmacokinetic/pharmacodynamic study in healthy volunteers after nasal delivery of midazolam (0.06mg/kg; 100-160 $\mu$ l into each nostril), using the midazolam formulation of Loftsson et al. (2001). Low mean peak serum levels of 42ng/ml within 10-15 minutes are observed, which are in the range of the reported threshold concentration for induction of sedation. Some sedative activity in the volunteers is shown for 1 hour after nasal administration. As stated before, the midazolam concentration used in the Loftsson formulation is not high enough to achieve optimal clinical effects.

The above mentioned plasma levels of midazolam are achieved by intranasal administration of the composition of the present invention, the dose of midazolam being selected to provide the plasma level which will result in the desired therapeutic effect. Preferably, the desired midazolam plasma level is achieved within 3 to 15 minutes of nasal administration of the composition.

The compositions of the present invention are preferably formulated for spray delivery, for example, by a pump spray device. Suitable devices which are already commercially available include multiple dose vials and bi-dose or unit-dose devices. The preferred devices are unit-dose devices and bi-dose devices. It is also possible to use disposable plastic unit-dose containers manufactured, for instance, by blow-fill-seal technology and known from commercial eye drops, to deliver a small volume of an intranasal midazolam formulation as a nasal liquid or nasal drops.

The composition of the present invention can also be administered in a liquid, semi-liquid, or semi-solid formulation for sublingual, buccal, rectal or any other transmucosal administration using a tampon, sponge, rectal or oromucosal capsule (i.e. a capsule for oromucosal absorption, such as buccal or sublingual mucosal absorption), mucosal patch, chewing gum, lollipop or any other form or device suitable for transmucosal drug delivery known to the skilled person, for example from the pharmaceutical literature.

According to a third aspect of the present invention, a device is provided, for spray delivery or delivery as liquid or nasal drops of a composition according to the first aspect of the present invention. The device preferably holds one or more doses of the composition.

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**Claims**

1. A pharmaceutical composition, which is a solution comprising midazolam in a concentration of at least 35mg/ml, and a solubilizer.  
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2. A composition as claimed in claim 1, wherein the concentration of midazolam is at least 40mg/ml.
3. A composition as claimed in claim 2, wherein the concentration of  
10 midazolam is at least 50mg/ml.
4. A composition as claimed in claim 1, wherein the concentration of midazolam is 35-75mg/ml.
- 15 5. A composition as claimed in any one of the preceding claims, wherein midazolam is used in the form of a pharmaceutically acceptable salt thereof.
6. A composition as claimed in claim 5, wherein the pharmaceutically acceptable midazolam salt is midazolam hydrochloride, midazolam maleate or  
20 midazolam lactate.
7. A composition as claimed in any one of the preceding claims, wherein the solution is an aqueous solution.
- 25 8. A composition as claimed in any one of the preceding claims, wherein the solubilizer comprises propylene glycol.
9. A composition as claimed in claim 8, wherein the solubilizer further comprises one or more of glycerol, polyethylene glycol, povidone, and ethanol.  
30
10. A composition as claimed in any one of claims 1-7, wherein the solubilizer comprises glycerol.

11. A composition as claimed in claim 10, wherein the solubilizer further comprises one or more of propylene glycol, polyethylene glycol, povidone, and ethanol.
- 5 12. A composition as claimed in any one of the preceding claims, wherein the pH of the composition is within the range of 2.5 to 7.
13. A composition as claimed in claim 12, wherein the pH of the composition is less than 4.
- 10 14. A composition as claimed in any one of the preceding claims, comprising 40-50% (v/v) propylene glycol and 50-60% (v/v) water.
- 15 15. A composition as claimed in claim 14, wherein the concentration of midazolam is 40-75 mg/ml.
16. A composition as claimed in any one of claims 14-15, comprising:  
midazolam in a concentration of 40-75 mg/ml,  
40-50% (v/v) propylene glycol, and  
20 50-60% (v/v) water,  
wherein the pH is adjusted to 2.5-4.
17. A composition as claimed in any one of claims 14-16 consisting of:  
midazolam in a concentration of 40-75 mg/ml,  
25 40-50% (v/v) propylene glycol, and  
50-60% (v/v) water, and  
and optionally a pharmaceutically acceptable acid or base in an amount sufficient to adjust the pH to 2.5-4.
- 30 18. A composition as claimed in any one of the preceding claims, which is adapted for intranasal delivery.

19. A composition as claimed in any one of claims 1-16, which is in the form of a spray or a nasal liquid or nasal drops.
20. A composition as claimed in any one of claims 1-17, which is adapted for sublingual, buccal, rectal or any other form of transmucosal administration.
21. A composition as claimed in any one of the preceding claims, for use as a sedative or anxiolytic agent, a medicament for administration to patients undergoing gastrointestinal endoscopy and other diagnostic procedures, a medicament for the treatment of acute epileptic and febrile seizures or for the acute management of seizures in patients suffering from epilepsy.
22. Use of a composition as claimed in any one of claims 1-20 for the manufacture of a sedative or anxiolytic agent, a medicament for administration to patients undergoing gastrointestinal endoscopy and other diagnostic procedures, a medicament for the treatment of acute epileptic and febrile seizures or for the acute management of seizures in patients suffering from epilepsy.
23. A use according to claim 22, wherein the composition is administered intranasally.
24. A use according to claim 22, wherein the composition is administered sublingually, buccally, rectally or in any other form of transmucosal administration.
25. A device for intranasal delivery comprising the composition as claimed in any one of claims 1-20.
26. A dosage form comprising the composition as claimed in any one of claims 1-20.
27. A dosage form as claimed in claim 26, wherein the dosage form is a tampon, sponge, rectal or oromucosal capsule, mucosal patch, chewing gum or lollipop.